REMARKS

Following entry of this amendment, claims 135 to 188 are pending in the application. Claims 1 to 134 have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of those claims in the future. Support for new claims 135 to 145 can be found in the specification, e.g., at page 3, lines 8 to 12 and 18 to 19; and at page 11, lines 5 to 11. Support for new claims 152, 170, and 188 can be found in the specification, e.g., at page 14, lines 8 to 12. Support for new claims 153 to 163 can be found in the specification, e.g., at page 3, line 29, to page 4, line 4; and at page 11, lines 5 to 11. Support for new claims 171 to 181 can be found in the specification, e.g., at page 3, lines 22 to 27; and at page 11, lines 5 to 11. Support for new claims 146 to 151, 163 to 169, and 182 to 187 can be found in the specification, e.g., at page 11, lines 17 to 23; and at page 13, lines 4 to 8. Claims 135 to 188 add no new matter.

The specification has been amended to replace the trade name "Neurontin" with the generic name "gabapentin" in paragraph [0027]. That amendment adds no new matter.

Pending Claims

Applicants note that the Examiner required an election of species to a single drug to be used in combination with milnacipran in an Office Action mailed May 16, 2008. The Examiner noted that

> [u]pon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 C.F.R. 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species.

See page 4. In response, applicants elected the species pregabalin. *See* Response to Restriction Requirement filed June 4, 2008, at page 1.

Applicants have canceled all of the previously pending claims without prejudice or disclaimer, and have added claims 135 to 188. Claims 135, 137, 146 to 153, 155, 164 to 171, 173, and 182 to 188 read on the elected species. Claims 135, 153, and 171 are generic.

Interview Summary

Applicants thank Examiner Hughes for the courtesy of the interview with applicants' representative Anthony Tridico on April 8, 2009. Applicants note that a copy of the Interview Summary prepared by the Examiner does not appear to have been scanned into the Image File Wrapper for this application on PAIR. Accordingly, applicants enclose a copy of that Interview Summary for scanning into the Image File Wrapper.

The following constitutes the Applicants' Statement of Interview Summary, pursuant to 37 C.F.R. § 1.133. Applicant's representative, Anthony Tridico, met with Examiner Alicia R. Hughes and Primary Examiner Raymond J. Henley, III, at the U.S. Patent and Trademark Office on April 8, 2009. At the interview, Dr. Tridico discussed the claims as amended herein and U.S. Patent No. 6,441,038 (Loder), which is currently cited against the application.[1] In particular, it was shown that Loder requires the *combination* of norepinephrine reuptake inhibitor (such as, for example, milnacipran) *and* a noradrenaline precursor, and therefore would not have rendered the pending claims obvious. Moreover, as explained herein, Loder teaches away from

[1] A copy of a PowerPoint presentation given at the interview is attached.

administration of milnacipran without a noradrenaline precursor. Certain administrative matters were also discussed, including applicants' discovery that a terminal disclaimer over U.S. Application No. 11/835,590 had not been filed.

Terminal Disclaimer

Applicants enclose a Terminal Disclaimer over U.S. Application No. 11/835,590. This Terminal Disclaimer should obviate the obviousness-type double patenting rejection over the '590 application made in the Office Action mailed September 28, 2007.

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 99, 101, 109, and 129 to 134 under 35 U.S.C. § 103(a) over Loder in view of U.S. Patent No. 6,500,853 (Seehra). Action at page 3. Specifically, the Examiner contended that

> While Loder et al do indeed [teach] combination therapy, though the Applicants construe the same to foreclose the instant reference from reading on the claims of the instant position, the office takes the contrary position that the same is motivation for combining drugs of similar known origin to treat fibromyalgia, pain and chronic fatigue syndrome.

Id. Seehra allegedly teaches pregabalin for treating pain, fibromyalgia, and chronic fatigue syndrome. *See* Office Action mailed September 5, 2008, at page 4. The Examiner further contended that "it would have been *prima facie* obvious to, upon determining the effectiveness of milnacipran and pregabalin to administer the same in combination with each other, to treat pain, fibromyalgia and chronic fatigue syndrome at the time that the instant invention was made." *Id.* at page 4.

Applicants respectfully traverse. Applicants have canceled claims 99, 101, 109, and 129 to 134 without prejudice or disclaimer. Applicants have added claims 135 to

188. As discussed above, claims 135, 137, 146 to 153, 155, 164 to 171, 173, and 182 to 188 read on the elected species of pregabalin. Applicants will therefore address the rejection with respect to those claims. Independent claims 135, 153, and 171 recite:

> 135. A method of treating fibromyalgia, **the method consisting essentially of** administering to a patient in need thereof an effective amount of at least one compound selected from milnacipran and a pharmaceutically acceptable salt thereof, and an effective amount of at least one additional compound selected from gabapentin, pregabalin, pramipexole, l-DOPA, tizanidine, clonidine, tramadol, morphine, codeine, and carbamazepine, and pharmaceutically acceptable salts thereof.
>
> 153. A method of treating chronic fatigue syndrome, **the method consisting essentially of** administering to a patient in need thereof an effective amount of at least one compound selected from milnacipran and a pharmaceutically acceptable salt thereof, and an effective amount of at least one additional compound selected from gabapentin, pregabalin, pramipexole, l-DOPA, tizanidine, clonidine, tramadol, morphine, codeine, and carbamazepine, and pharmaceutically acceptable salts thereof.
>
> 171. A method of treating pain, **the method consisting essentially of** administering to a patient in need thereof an effective amount of at least one compound selected from milnacipran and a pharmaceutically acceptable salt thereof, and an effective amount of at least one additional compound selected from gabapentin, pregabalin, pramipexole, l-DOPA, tizanidine, clonidine, tramadol, morphine, codeine, and carbamazepine, and pharmaceutically acceptable salts thereof.

(Emphasis added). Claims 137 and 146 to 152 ultimately depend from claim 135. Claims 155 and 164 to 170 ultimately depend from claim 153. Claims 173 and 182 to 188 ultimately depend from claim 171.

To establish a *prima facie* case of obviousness, there must be some reason for one skilled in the art to modify a document or combination of documents to arrive at the claimed invention. *See, e.g.*, MPEP § 2143. The mere fact that a document can be modified does not render the resulting modification obvious unless the results would have been predictable to one of ordinary skill in the art. *See* MPEP § 2143.01(III) (citing

KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385, 1396 (2007)). Furthermore, when the prior art teaches away from making a particular modification, that modification is more likely to be nonobvious. *See, e.g., KSR Int'l Co.*, 82 USPQ2d at 1395.

As discussed in detail below, one skilled in the art would have had *no reason* to remove the noradrenaline precursor from Loder's combinations. Loder expressly teaches that administering a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor is much less effective than the combination. In fact, Loder *teaches away* from using a noradrenaline reuptake inhibitor alone by proposing a specific mechanism to explain why the combinations are so much more effective. Thus, as will be explained below, applicants assert that Loder would have failed to render obvious the use of a noradrenaline reuptake inhibitor *in the absence* of a noradrenaline precursor.

One skilled in the art would have had no reason to use a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor based on Loder

Each of the independent claims excludes methods in which milnacipran is administered with an additional compound other than those recited in the claim. Loder, however, only discusses a method involving administration of a noradrenaline reuptake inhibitor in combination with a noradrenaline precursor such as phenylalanine or tyrosine. Specifically, Loder is directed to

> [a] method of treatment of disorders of neurological origin and drug formulations for use in the method. . . . The treatment comprises administering to a patient in need thereof **a selective inhibitor of noradrenaline reuptake combined with either phenylalanine or tyrosine** in the same dosage formulation or the same pack.

See Abstract (emphasis added).

Throughout the specification, Loder emphasizes that it is the combination of noradrenaline reuptake inhibitors with noradrenaline precursors that is the subject of the invention. Loder discusses, for example, "[o]ther drugs which are effective **in combination with** phenylalanine or tyrosine are drugs which are combined inhibitors of both noradrenaline and serotonin uptake...." Col. 1, lines 42 to 44 (emphasis added). Loder also discusses a "list of possible uses **of the combinations**..." (col. 1, line 50 (emphasis added)) and "[a] particularly important new use **for the combinations**..." (col. 1, lines 57 to 58 (emphasis added)).

In assessing the effectiveness of the combinations, Loder indicates that

> [t]he anecdotal evidence indicating that **noradrenaline precursors and noradrenergic drugs** like lofepramine and desipramine are particularly effective, and the new and unexpected clinical trial evidence which clearly proves efficacy.... In particular, **the combination of** noradrenaline precursors, phenylalanine and tyrosine, coupled with a drug which either has its sole action or a component of its action the inhibition of noradrenaline reuptake, is now seen to be valuable in the treatment of fatigue in any form, in the management of rehabilitation after stroke, in the treatment of stress in any form, and in the treatment of fibromyalgia and related disorders such as irritable bowel syndrome.

Col. 3, lines 13 to 28 (emphasis added). Loder further asserts the combination of a noradrenaline reuptake inhibitor with a noradrenaline precursor is specifically responsible for that effectiveness:

> These effects of noradrenergic compounds alone are important but relatively modest. **Our concept of combining** a noradrenergic drug like lofepramine or desipramine, together with a noradrenaline precursor such as phenylalanine or tyrosine, **is much more effective**."

Col. 6, lines 36 to 40 (emphasis added).

Thus, based on the teachings of Loder, one skilled in the art would have had *no reason* to administer milnacipran in the absence of a noradrenaline precursor.

Loder explicitly teaches away from the use of a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor

Not only would one skilled in the art have had no reason to modify Loder by removing the noradrenaline precursor required for the effectiveness of his combinations, Loder goes even further - he teaches away from the claimed invention in his explanation of the mechanism of action of the combinations. Specifically, to explain his observations, Loder proposes a mechanism that requires the combined effect of increasing noradrenaline synthesis and decreasing noradrenaline uptake. *See* col. 6, lines 56 to 66. According to Loder, that mechanism

> ...is the explanation **for the strong interaction** we have observed between lofepramine and phenylalanine. In MS, the LC and LT noradrenergic systems are activated and stressed leading to loss of the feedback control of noradrenaline synthesis. As a result **phenylalanine can enhance noradrenaline synthesis and *strongly interact* with lofepramine which inhibits uptake of released noradrenaline and so activates noradrenergic systems**.

Col. 6, line 62, to col. 7, line 3 (emphasis added). Furthermore, according to Loder, the described combinations had not previously been proposed because the mechanism was not appreciated:

> **Because of a failure to understand this unique mechanism**, although it has been proposed that phenylalanine and tyrosine may be used to treat depression, **it has never been proposed that phenylalanine or tyrosine should be specifically combined with drugs which have specific effects on noradrenaline reuptake** such as lofepramine, desipramine and reboxetine. Such combinations will be particularly effective in treating depression, especially when that depression is associated with chronic stress and abnormal function of the LC and LT systems.

Col. 7, l. 61, to col. 8, l. 3 (emphasis added).

Finally, Loder provides a clinical example that teaches that noradrenaline reuptake inhibitors used alone are ineffective for treating fibromyalgia and chronic

fatigue syndrome. In Case History No. 1, Loder describes a 41 year old woman who had suffered from chronic fatigue syndrome associated with fibromyalgia and irritable bowel syndrome for 12 years. *See* col. 5, lines 39 to 65. According to Loder,

> [s]he was given almost all conceivable treatments over the years including ... noradrenaline reuptake inhibiting antidepressants.... Some of these treatments produced transient effects but these never lasted. **She was then given combined treatment** with lofepramine, 70 mg bd and L-phenylalanine, 500 mg bd. Over a period of 2-3 weeks she experienced a considerable improvement in fatigue, in fibromyalgia and in her irritable bowel.... **After six months she was essentially back to her normal self.**"

Id., lines 53 to 65 (emphasis added).

Thus, applicants assert that Loder's invention is based on his "unique mechanism," which dictates the use of a noradrenaline precursor in combination with a noradrenergic drug. In fact, Loder's Case History No. 1 specifically teaches that noradrenergic drugs used alone are ineffective. Thus, Loder teaches away from a method that involves administering a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor.

In sum, considering Loder, one skilled in the art would have had no reason to modify Loder's combinations by removing the noradrenaline precursor, and furthermore, Loder explicitly teaches away from making such a modification. Accordingly, Loder would have failed to render obvious a method involving administering a noradrenaline reuptake inhibitor in the absence of a noradrenaline precursor.

Applicants assert that Seehra would have failed to remedy the deficiencies of Loder. That is, Seehra would have given one skilled in the art no reason to remove the required noradrenaline precursor from the combinations of Loder. Pregabalin, which is discussed in Seehra, is not a noradrenaline precursor, and therefore would not have

substituted for the removed compound. Because Seehra would have failed to remedy the deficiencies of Loder, applicants need not address the Examiner's contentions with respect to Seehra and certain elements of the claims. By not addressing those contentions, applicants in no way acquiesce to them.

In conclusion, applicants assert that the combination of Loder and Seehra would not have rendered the pending claims obvious for at least the reasons discussed above. Applicants therefore respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Loder in view of Seehra.

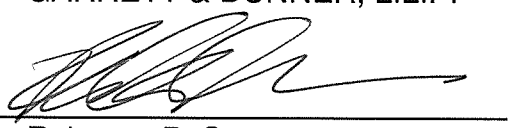
Applicants respectfully assert that the present application is in condition for allowance and request that the Examiner issue a timely Notice of Allowance.

Please grant any extensions of time required to enter this Amendment and Response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 17, 2009

By: 

Rebecca B. Scarr
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Interview Summary	Application No.	Applicant(s)	
	10/623,431	KRANZLER ET AL.	
	Examiner	Art Unit	
	ALICIA R. HUGHES	1614	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ALICIA R. HUGHES*. (3)*Anthony Tridico*.

(2) *Raymond Henley, III*. (4)_____.

Date of Interview: *08 April 2009*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *Powerpoint presentation made by Applicants' representative*.

Claim(s) discussed: *99,109,119 and 129-134*.

Identification of prior art discussed: *U.S. Patent No. 6,441,038 ["Loder et al"]*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *At the core of the interview was whether Loder et al teaches away from the claimed invention based on the required combination of milnacipran with another active ingredient and the fact that the combination is actually required by the reference in order to work in the treatments described therein. Administrative matters such as the need to file terminal disclaimers, etc. was also discussed.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

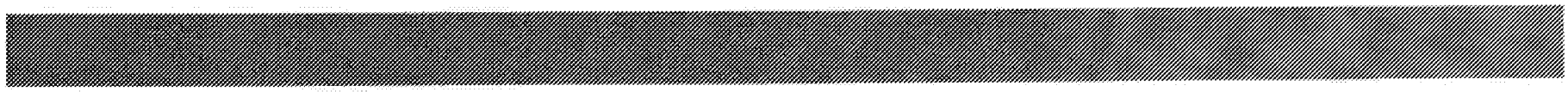
/Alicia R. Hughes/
Examiner, Art Unit 1614

Bulletin

Finnegan, Henderson, Farabow, Garrett & Dunner, LLP

Examiner Interview
April 8, 2009

U.S. Application Nos. 10/623,431;
11/752,213; and 12/035,820



ISSUED CLAIMS

- U.S. Patent No. 6,602,911
  1. A method of treating **fibromyalgia** syndrome (FMS) comprising administering to an animal subject suffering from FMS, a composition **wherein the active ingredient consists of milnacipran**, or a pharmaceutically acceptable salt thereof in an amount effective to treat the chronic pain and fatigue associated with FMS.

ISSUED CLAIMS

- U.S. Patent No. 6,635,675
  1. A method of treating **chronic fatigue syndrome** (CFS) comprising administering to an animal subject suffering from CFS, a composition **wherein the active ingredient consists of milnacipran**, or a pharmaceutically acceptable salt thereof in an amount effective to treat pain or fatigue associated with CFS.

ISSUED CLAIMS

- U.S. Patent No. 6,992,110
  1. A method of treating **pain** in an animal subject, comprising administering to an animal subject suffering from pain, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, **alone or in combination with a compound that is not phenylalanine, tyrosine or tryptophan**.

PROPOSED CLAIMS

- U.S. Application No. 11/752,215

  41. A method of treating **fibromyalgia**, **the method consisting essentially of** administering to a patient in need thereof an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof.

'911 patent:

1. A method of treating **fibromyalgia** syndrome (FMS) comprising administering to an animal subject suffering from FMS, a composition **wherein the active ingredient consists of milnacipran**, or a pharmaceutically acceptable salt thereof in an amount effective to treat the chronic pain and fatigue associated with FMS.

PROPOSED CLAIMS

- U.S. Application No. 10/623,431

  135. A method of treating **fibromyalgia**, **the method consisting essentially of** administering to a patient in need thereof an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, and an effective amount of at least one additional compound selected from gabapentin, pregabalin, pramipexole, l-DOPA, tizanidine, clonidine, tramadol, morphine, codeine, and carbamazepine, and pharmaceutically acceptable salts thereof.

'911 patent:

1. A method of treating **fibromyalgia** syndrome (FMS) comprising administering to an animal subject suffering from FMS, a composition **wherein the active ingredient consists of milnacipran**, or a pharmaceutically acceptable salt thereof in an amount effective to treat the chronic pain and fatigue associated with FMS.

PROPOSED CLAIMS

- U.S. Application No. 10/623,431

  152. A method of treating **chronic fatigue syndrome**, **the method consisting essentially of** administering to a patient in need thereof an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, and an effective amount of at least one additional compound selected from gabapentin, pregabalin, pramipexole, l-DOPA, tizanidine, clonidine, tramadol, morphine, codeine, and carbamazepine, and pharmaceutically acceptable salts thereof.

'675 patent:

1. A method of treating **chronic fatigue syndrome** (CFS) comprising administering to an animal subject suffering from CFS, a composition **wherein the active ingredient consists of** milnacipran, or a pharmaceutically acceptable salt thereof in an amount effective to treat pain or fatigue associated with CFS.

PROPOSED CLAIMS

- U.S. Application No. 10/623,431

169. A method of treating **pain**, **the method consisting essentially of** administering to a patient in need thereof an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, and an effective amount of at least one additional compound selected from gabapentin, pregabalin, pramipexole, l-DOPA, tizanidine, clonidine, tramadol, morphine, codeine, and carbamazepine, and pharmaceutically acceptable salts thereof.

'110 patent:

1. A method of treating **pain** in an animal subject, comprising administering to an animal subject suffering from pain, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, **alone or in combination with a compound that is not phenylalanine, tyrosine or tryptophan**.

PROPOSED CLAIMS

- U.S. Application No. 12/035,820

  57. A method of treating **pain**, **the method consisting essentially of** orally administering to a patient in need thereof an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof.

'110 patent:

1. A method of treating **pain** in an animal subject, comprising administering to an animal subject suffering from pain, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, **alone or in combination with a compound that is not phenylalanine, tyrosine or tryptophan**.

PROPOSED CLAIMS

- U.S. Application No. 12/035,820

65. A method of treating **neuropathic pain**, **the method consisting essentially of** orally administering to a patient in need thereof an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof.

78. A method of treating **chronic pain**, **the method consisting essentially of** orally administering to a patient in need thereof an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof.

'110 patent:

1. A method of treating **pain** in an animal subject, comprising administering to an animal subject suffering from pain, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, **alone or in combination with a compound that is not phenylalanine, tyrosine or tryptophan**.

- Terminal Disclaimers

  See Terminal Disclaimer chart

  – U.S. Application No.10/623,431 (fibromyalgia, CFS, pain)
    - TDs already filed, except no TD filed over 11/835,590

  – U.S. Application No. 11/752,213 (fibromyalgia)
    - TDs not yet filed
    - Consider DP with respect to '911 patent

  – U.S. Application No. 12/035,820 (pain)
    - TDs not yet filed
    - Consider DP with respect to '431 application

- U.S. Application No. 11/752,213
  - Should be identified as a CIP of 10/623,431
  - Will amend specification and file new Declaration

Loder et al., U.S. Patent No. 6,441,038 B1

TREATMENT OF FATIGUE, HEAD INJURY AND STROKE

"A method of treatment of disorders of neurological origin and drug formulations for use in the method are disclosed. . . . The treatment comprises administering to a patient in need thereof a selective inhibitor of noradrenaline reuptake **combined with** either phenylalanine or tyrosine in the same dosage formulation or the same pack."

Loder at Abstract

Loder only teaches a noradrenaline reuptake inhibitor **in combination with** a noradrenaline precursor

"The treatment comprises administering to a patient in need thereof a selective inhibitor of noradrenaline reuptake **combined with** either phenylalanine or tyrosine in the same dosage form of the same pack." Abstract.

"Other drugs which are effective **in combination with phenylalanine or tyrosine** are drugs which are combined inhibitors of both noradrenaline and serotonin uptake...." Col. 1, ll. 42-45.

"In addition to refining the list of the most effective drugs, the list of possible uses **of the combinations** has been expanded to include...." Col. 1, ll. 49-51.

Loder only teaches a noradrenaline reuptake inhibitor **in combination with** a noradrenaline precursor

"The anecdotal evidence indicating that noradrenaline precursors **and** noradrenergic drugs like lofepramine and desipramine are particularly effective, and the new and unexpected clinical trial evidence which clearly proves efficacy.... **In particular, the combination of** noradrenaline precursors, phenylalanine and tyrosine, coupled with a drug which either has its sole action or a component of its action the inhibition of noradrenaline reuptake, is now seen to be valuable in the treatment of...." Col. 3, ll. 13-28.

"These effects of noradrenergic compounds alone are important but relatively modest. **Our concept of combining** a noradrenergic drug like lofepramine or desipramine, together with a noradrenaline precursor such as phenylalanine or tyrosine, **is much more effective**." Col. 6, ll. 36-40.

Loder's proposed mechanism involves **the combined effect** of increasing noradrenaline synthesis ***and*** decreasing noradrenaline uptake. *See* col. 6, ll. 56-66.

"We propose that this is the explanation **for the strong interaction** we have observed between lofepramine and phenylalanine. In MS, the LC and LT noradrenergic systems are activated and stressed leading to loss of the feedback control of noradrenaline synthesis. As a result **phenylalanine can enhance noradrenaline synthesis and *strongly interact* with lofepramine which inhibits uptake of released noradrenaline and so activates noradrenergic systems**." Col. 6, l. 62, to col. 7, l. 3.

PRIOR ART

MECHANISM

Phenylalanine

↓

Tyrosine

↓ Tyrosine hydroxylase

3-dihydroxyphenylalanine

↓

Dopamine

↓

Noradrenaline

Col. 7, ll. 43-53.

This unique mechanism thus activates the brain LC and LT systems particularly well when there is a need for activation as demonstrated by removal of the feedback inhibition of noradrenaline synthesis. In contrast, in normal situations when feedback inhibition is fully operative, the combination will not exert adverse effects because then the phenylalanine or tyrosine will not be able to enhance noradrenaline synthesis. **Because of a failure to understand this unique mechanism**, although it has been proposed that phenylalanine and tyrosine may be used to treat depression, **it has never been proposed that phenylalanine or tyrosine should be specifically combined with drugs which have specific effects on noradrenaline reuptake such as lofepramine, desipramine and reboxetine.** Such combinations will be particularly effective in treating depression, especially when that depression is associated with chronic stress and abnormal function of the LC and LT systems. Col. 7, l. 54, to col. 8, l. 3.

Loder explicitly teaches that noradrenergic drugs used alone are ineffective for treating fibromyalgia and CFS.

Case History No. 1: 41 year old with CFS associated with fibromyalgia and IBS for 12 years.

"**She was given almost all conceivable treatments over the years including** many types of [NSAIDS] and serotonin reputake inhibiting and **noradrenaline reuptake inhibiting antidepressants**, and even steroids. Some of these treatments produced **transient effects** but these **never lasted**. **She was then given combined treatment** with lofepramine, 70 mg bd and L-phenylalanine, 500 mg bd. Over a period of 2-3 weeks she experienced a considerable improvement in fatigue, in fibromyalgia and in her irritable bowel.... **After six months she was essentially back to her normal self.**" Col. 5, ll. 39-65.

- Loder teaches away from using a noradrenergic drug in the absence of a noradrenaline precursor
  - Loder's invention is based on his "unique mechanism," which dictates the use of a noradrenaline precursor ***in combination with*** a noradrenergic drug.
  - Considering Loder, one skilled in the art would have had no reason to remove the noradrenaline precursor from Loder's combinations. In fact, Loder's Case History No. 1 specifically teaches that noradrenergic drugs used alone are ineffective.

EXEMPLARY PROPOSED CLAIMS

- U.S. Application No. 11/752,215

  41. A method of treating **fibromyalgia**, **the method consisting essentially of** administering to a patient in need thereof an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof.

  → The method does not encompass administering milnacipran with a noradrenaline precursor

'911 patent:

1. A method of treating **fibromyalgia** syndrome (FMS) comprising administering to an animal subject suffering from FMS, a composition **wherein the active ingredient consists of milnacipran**, or a pharmaceutically acceptable salt thereof in an amount effective to treat the chronic pain and fatigue associated with FMS.

EXEMPLARY PROPOSED CLAIMS

- U.S. Application No. 10/623,431

135. A method of treating **fibromyalgia**, **the method consisting essentially of** administering to a patient in need thereof an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, and an effective amount of at least one additional compound selected from gabapentin, pregabalin, pramipexole, l-DOPA, tizanidine, clonidine, tramadol, morphine, codeine, and carbamazepine, and pharmaceutically acceptable salts thereof.

→ The method does not encompass administering milnacipran with a noradrenaline precursor (and at least one additional compound).